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Disease Etiology Impact on Outcomes of Hepatocellular Carcinoma Patients Treated with Atezolizumab plus Bevacizumab: A Real-World, Multicenter Study

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Keywords

Hepatocellular carcinoma · Atezolizumab · Bevacizumab · Immunotherapy · Etiology · Non-alcoholic steatohepatitis · Viral hepatitis

Abstract

Introduction: The impact of etiology on response to immunotherapy in advanced hepatocellular carcinoma (HCC) is being debated, with contrasting findings between early and recent post hoc analyses of IMbrave-150 and metanalyses of clinical trials of PD-1/PD-L1 blockers. As a results, it is not clear whether the first-line systemic treatment atezolizumab plus bevacizumab (A + B) is equally effective in viral and nonviral patients. ***Methods:*** We retrospectively analyzed 885 HCC patients treated with the first-line A + B from multiple centers from Eastern and Western countries, 53.9% having viral and 46.1% nonviral etiology. Baseline clinical and laboratory characteristics were analyzed with uni- and multivariate models to explore potential differences on overall survival (OS), time-to-progression (TTP), disease control rates (DCRs) based on etiology and to identify putative prognostic factors in etiology subgroups. Treatment toxicities and access to the second-line treatments and outcomes were also reported and compared between etiologies. ***Results:*** Overall, no statistically significant differences were found in median OS (mOS: viral 15.9 months; nonviral 16.3 months), TTP (mTTP: viral 8.3 months; nonviral 7.2 months), and DCRs (viral 78.1%; nonviral 80.8%) based on etiology. Prognostic factors of survival and progression were mainly shared between viral and nonviral etiologies, including alpha-fetoprotein, aspartate transaminase, neutrophil-to-lymphocyte ratio (NLR) and ALBI score. Exploratory analyses highlighted a possible stronger association of immunological factors, i.e., NLR and eosinophil count,

to treatment outcomes in viral patients. The toxicity profile, the access to and type of the second-line treatments and their outcome in terms of OS almost overlap in the two etiology subgroups. ***Conclusion:*** Atezolizumab plus bevacizumab efficacy does not vary according to underlying etiology of HCC in a multicenter, real-world population, matching recent post hoc findings from the IMbrave-150 trial. Preliminary analyses suggest that some prognostic factors differ between viral and nonviral patients, potentially due to biological and immunological differences. Prospective and comparative trials stratifying by etiology are warranted to validate these findings and guide clinical practice.

Introduction

Understanding the impact of etiology on response to treatment in advanced hepatocellular carcinoma (HCC) has recently taken central stage following approval of immunotherapeutic approaches in first-line [1]. Initial trials suggested that the etiology of liver disease could serve as a predictive marker for the efficacy of immune checkpoint inhibitors (ICIs) targeting the programmed death protein/ligand 1 (PD-1/PD-L1) axis [2–4]. However, as more clinical data emerged, the association between etiology and response to PD-1/PD-L1 blockade has been questioned [5, 6].

The subgroup analysis of the IMbrave-150 trial provided initial evidence of etiology playing a role in the response to ICI therapy [2, 4]. The trial demonstrated an overall survival (OS) advantage for the combination of the anti-PD-L1 atezolizumab plus the anti-vascular/endothelial growth factor bevacizumab (A + B) compared to sorafenib, but the nonviral subgroup showed less favorable results compared to the hepatitis B (HBV) and C (HCV) cohorts. Oppositely, retrospective data on large real-world data suggest a possible higher efficacy of the tyrosine-kinase inhibitor lenvatinib in patients with underlying metabolic liver disease [7–9].

A subsequent metanalysis incorporating data from IMbrave-150, comparing A + B versus sorafenib in first-line [2, 4]; CheckMate-459, comparing the anti-PD-1 nivolumab versus sorafenib in first-line [10]; and Keynote-240, comparing the anti-PD-1 pembrolizumab plus best supportive care (BSC) versus placebo plus BSC in second line [3], concluded that immunotherapy was superior to control treatments in viral etiology patients but did not provide a survival advantage in nonviral etiology ones [11]. In the same work, the authors established a preclinical model of non-alcoholic steatohepatitis (NASH)-related HCC highlighting CD8+ T cells contribution in the development of HCC rather than in executing immune surveillance, resulting also resistant to PD-1 blockade.

However, a more recent post hoc analysis of the IMbrave-150 carried out exclusively in the subgroup of patients treated with A + B showed no differences in terms of objective response rate, progression-free survival, and OS based on etiology [5]. Additionally, a recent metanalysis of eight immunotherapy clinical trials concluded that immunotherapy could provide an OS advantage over control treatments also in nonviral patients [6].

In the present study, we retrospectively interrogated a large real-world population of HCC patients from Asia and Europe treated with A + B for possible differences in hard outcomes (i.e., OS, time-to-progression and DCRs) and in prognostic factors based on etiology of underlying liver disease to consolidate the findings of the IMbrave-150 post hoc analysis [5] in a real-world scenario.

Materials and Methods

Study Population

Patients with advanced-stage HCC (Barcelona Clinic Liver Cancer stage C, BCLC-C) or intermediate HCC (BCLC-B) who were ineligible for first- or re-treatment with surgical or locoregional therapies and received A + B as the first-line systemic therapy were included in the study population. Between May 2020 and April 2022, the overall cohort included Western and Eastern populations from 42 centers in five countries (Italy, Germany, Portugal, Japan, and the Republic of Korea), with data for analysis collected retrospectively. Most of the patients were from Asia (n = 791, 89% of the total, of which 715 from Japan and 76 from Republic of Korea), while the rest were from Europe (n = 94, 11% of the total, of which 44 from Italy, 35 from Germany and 15 from Portugal; online suppl. Fig. 1; for all online suppl. material, see https://doi.org/10.1159/000537915).

Patients who were eligible had their HCC diagnoses confirmed histologically or by imaging criteria according to international guidelines, and none had previously received systemic therapy. Ages at treatment start ranged from 27 to 94 years, with a median of 72 years and interquartile range 65-to-78 years. Both sexes were included in the study population, with 79.7% of males and 20.3% of females. Median body mass index was 23.4 kg/m^2, with an interquartile range of 21.1-to-25.8 kg/m^2.

The current study was approved by the Ethics Committees at each center, and it followed the Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws, as well as the European Parliament and Council Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data, which was enacted on April 27, 2016.

Treatments and Definitions

A + B was administered as described in the IMbrave-150 trial (1,200 mg of atezolizumab plus 15 mg per kilogram of body weight of bevacizumab intravenously every 3 weeks) [2].

Treatment interruptions and dose reductions were allowed to manage adverse events (AEs) as per local practice. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Patients were followed every 2–3 months with multiphasic scanning technique, based on clinical practice of the center. Tumor assessment was carried out regardless of dose interruption until radiological disease progression. When progression was diagnosed according to mRECIST criteria, the adoption of any subsequent anticancer medication depended on the local physician decision.

The Clinical Practice Guidelines of the European Associations for the Study of the Liver, the Study of Diabetes and the Study of Obesity were used as reference to define the NASH/non-alcoholic fatty liver disease (NALFD) population and NAFLD-related HCC [12–14] as follows:

- Presence of steatosis in >5% of hepatocytes according to histological analysis.
- Patients without a history of alcohol abuse (≥30 g for men and ≥20 g for women).
- HBV and HCV negativity.

Prior definitions were maintained in place of the more recent one of metabolic associated steatohepatitis and metabolic associated steatotic liver disease due to its unavailability at the time of data collection from each of the 42 involved centers and the incomplete overlapping of the different definitions [14]. HBV and HCV etiologies were assigned to those patients with demonstrated prior or ongoing respective infection.

Patients with alcohol history (defined as alcohol consumption of ≥30 g per day in men or ≥20 g in women) and/or that cannot be classified in one of the three above categories were considered as "other" etiologies. For patients with multiple etiologies, we used a trumping algorithm and prioritized etiology as HBV > HCV > NASH/NAFLD or other.

Statistical Analysis

Categorical variables were reported as the number of cases and percentage, continuous variables were expressed as median and 95% confidence interval (CI). OS was computed as the interval between the date of therapy start until the date of death for any reason. Time-to-progression (TTP) was defined as the time from the start date of treatment to the date of progression or last follow-up. OS and TTP were reported as median values expressed in months, with 95% CI Survival curves were estimated using the product-limit method of Kaplan-Meier. The role of stratification factors was analyzed using log-rank tests applying the Bonferroni's correction when more than two factors were evaluated.

Hazard ratios (HRs) in multivariate analysis of baseline characteristics were calculated using the Cox proportional-hazards regression model. Differences in baseline characteristics between groups were estimated with Mann-Whitney test, Fisher's exact test, or χ^2 test, as specified in the Results section.

Continuous variables were dichotomized using receiver operating characteristic (ROC) curves applying the survival either above or below the mean OS as classification variable to identify a possibly prognostic cutoff value based on the Youden's index in case of area under the curve > 0.5 and $p < 0.05$, unless a cutoff value with a prognostic role has already been described. About the latter case, cutoff for albumin was set at 3.5 g/dL and α-fetoprotein (AFP) at 400 mg/mL according to [15–20], respectively. A MedCalc package (MedCalc® version 16.8.4) was used for statistical analyses.

Results

Patients' Characteristics

Data from $n = 885$ HCC patients treated with A + B as the first-line systemic therapy were analyzed. Of them, $n = 477$ had underlying viral etiology (53.9%; $n = 206$ HBV-related, 23.3% of total; $n = 271$ HCV-related, 30.6% of total) and $n = 408$ nonviral one (46.1%; $n = 197$ with NASH/NAFLD, 22.3% of total; $n = 211$ with other etiologies, 23.8% of total) (Table 1).

Different etiologies were similarly represented in subgroups of geographical origin, except made for HBV predominance in patients from Republic of Korea (75%) and other etiologies (including alcohol) in patients from Portugal (47%) (online suppl. Fig. 1A). In the viral etiology group, the median follow-up time was 10.3 months (95% CI: 9.2–42.0 months), the median TTP (mTTP) 8.3 months (95% CI: 6.7–9.7 months) and the median OS (mOS) 15.9 months (95% CI: 14.5–23.9 months). In the nonviral etiology group, the median follow-up time was 10.6 months (95% CI: 9.1–41.9 months), the mTTP 7.2 months (95% CI: 6.2–8.6 months), and the mOS 16.3 months (95% CI: 13.7–17.0 months). Baseline clinical and laboratory characteristics of patients with viral and nonviral etiologies treated with A + B are depicted in Table 2.

Disease Outcomes Do Not Differ in HCC Patients with Diverse Etiologies Treated with Atezolizumab plus Bevacizumab

We performed Kaplan-Meier OS analysis of HCC patients grouped for underlying etiology and found no statistically significant differences among them (HBV mOS 15.7, 95% CI 13.5–19.0 months; HCV mOS 15.9, 95% CI 14.2–23.9 months; NASH/NAFLD mOS 15.7, 95% CI 12.2–16.8 months; other etiologies mOS 16.3, 95% CI 14.6–22.5 months; $p = 0.8734$) (Fig. 1a; online suppl. Table 1). Similarly, no differences in TTP were detected (HBV mTTP 8.5, 95% CI 6.5–10.5 months; HCV mTTP 7.6, 95% CI 6.5–10.1 months; NASH/NAFLD mTTP 6.2, 95% CI 5.2–8.8 months; others mTTP 7.9, 95% CI 6.7–9.0 months; $p = 0.5393$) (Fig. 1b; online suppl. Table 1).

We then evaluated the response rates according to mRECIST criteria across liver disease etiologies to

Table 1. Representation of different etiologies in the study population

Etiology	Patients, *n* (% of total)	Etiology (grouped)	Patients, *n* (% of total)
HCV	271 (30.6)	Viral	477 (53.9)
HBV	206 (23.3)		
NASH/NAFLD	197 (22.3)	Nonviral	408 (46.1)
Other	211 (23.8)		

determine antitumor effects directly attributed to treatment. The fraction of patients who achieved complete responses (CRs), partial responses (PRs), stable disease (SD), and progressive disease (PD) differed between patients with HCV etiology (6.8%, 25.7%, 44.2%, 23.3%, respectively) and HBV etiology (4.1%, 16.6%, 59.1%, 20.2%, respectively; χ^2 test, $p = 0.0130$) and between those with HCV and other etiologies (2.1%, 26.3%, 55.2%, 16.5%, respectively; χ^2 test, $p = 0.0154$), while was similar in all other comparisons including those with NASH/NAFLD etiology (3.2%, 23.0%, 51.9%, 21.9%, respectively; χ^2 tests, $p > 0.05$). In terms of DCR, defined as the fraction of patients that achieved CR, PR, or SD as best response to treatment, no significant difference was observed between viral and non-viral patients ($p = 0.3457$, χ^2 test on DCR, Fig. 1e).

By grouping viral and nonviral etiologies, no significant differences were found in neither the respective OS (viral mOS 15.9, 95% CI 14.9–23.9 months; nonviral mOS 16.3, 95% CI 13.7–17.0 months; HR 0.93, 95% CI 0.73–1.18, $p = 0.5464$) (Fig. 1c) nor TTP (viral mTTP 8.3, 95% CI 6.7–9.7 months; nonviral mOS 7.2, 95% CI 6.2–8.6 months; HR 0.92, 95% CI 0.77–1.11, $p = 0.4030$) (Fig. 1d). In terms of DCR, viral patients achieved 5.7% of CR, 21.7% of PR, 50.7% of SD (DCR 78.1%), whereas nonviral one 2.6% of CR, 24.7% of PR and 53.5% of SD (DCR 80.8%) ($p = 0.3430$, Fisher's test on DCR, Fig. 1f).

Baseline Clinical and Laboratory Prognostic Factors of Survival in HCC Patients Treated with Atezolizumab plus Bevacizumab according to Viral and Nonviral Etiologies

At univariate analysis, the risk of death of HCC patients treated with the first-line A + B regardless of etiology (online suppl. Fig. 1B, C; Table 2) was reduced in Child-Pugh A patients compared to B ones (HR 0.07, $p < 0.0001$), BCLC class B compared to C (HR 0.74, $p = 0.0189$), ECOG PS 0 compared to 1 (HR 0.73, $p = 0.0120$), lymphocyte count ≥950/μL (HR 0.66, $p = 0.0032$), neutrophil-to-lymphocyte ratio (NLR) <3 (HR 0.57, $p = 0.0001$), eosinophil count ≥70/μL (HR 0.36, $p = 0.0007$), AFP <400 ng/mL (HR 0.47, $p = 0.0001$), serum albumin ≥3.5 g/dL (HR 0.30, $p = 0.0001$), serum bilirubin <1 mg/dL (HR 0.74, $p = 0.0223$), ALBI score 1 (HR 0.11, $p < 0.0001$), AST <65 U/L (HR 0.32, $p < 0.0001$), ALT <40 U/L (HR 0.65, $p = 0.0017$), ALP ≤125 U/L (HR 0.50, $p = 0.0005$), previous surgery (HR 0.72, $p = 0.0118$), and absence of portal vein thrombosis or major vascular invasion (HR 0.55, $p < 0.0001$).

We performed a multivariate analysis incorporating all independent baseline variables that (1) were significantly associated to a reduced risk of death in univariate analysis, (2) were differently represented in viral and nonviral patients (see Table 2), and (3) had available data for ≥750 patients (see Table 2). Of these, AFP <400 ng/mL (HR 0.64, $p = 0.0016$), AST <65 U/L (HR 0.54, $p = 0.0005$), NLR <3 (HR 0.61, $p = 0.0002$), and ALBI grade 1 (HR 0.30 $p < 0.0001$), but not viral versus nonviral etiology (HR 1.02, $p = 0.8830$) resulted as prognostic markers of OS (Fig. 2a; online suppl. Table 3).

Univariate (online suppl. Fig. 1; Table 2) and multivariate (Fig. 2; online suppl. Table 3) sub-analyses of baseline clinical and laboratory variables in viral and nonviral populations retrieved overlapping results to the overall population, with the sole exception of AFP <400 ng/mL in nonviral patients being borderline significant (HR 0.69, $p = 0.0953$).

When considering the risk of progression of the overall HCC population treated with the first-line A + B, risk reduction was observed in univariate analysis in patients with Child-Pugh A compared to B (HR 0.50, $p = 0.0019$), BCLC class B compared to C (HR 0.81, $p = 0.0326$), BMI >18.5 (HR 0.50, $p < 0.0001$), NLR <3 (HR 0.70, $p = 0.0003$), eosinophil count ≥70/μL (HR 0.36, $p < 0.0001$), AFP <400 ng/mL (HR 0.61, $p < 0.0001$), serum albumin ≥3.5 g/dL (HR 0.55, $p < 0.0001$), ALBI score 1 (HR 0.54, $p = 0.0017$), AST <65 U/L (HR 0.57, $p < 0.0001$), ALT <40 U/L (HR 0.81, $p = 0.0449$), ALP ≤125 U/L (HR 0.73, $p = 0.0366$), previous

Table 2. Baseline characteristics of the study populations

Variable	Total (n = 885)	Viral (n = 477)	Nonviral (n = 408)	p value	Test
Clinical					
Sex, n (%)				0.1113	Fisher
Male	705 (79.7)	370 (77.6)	335 (82.1)		
Female	180 (20.3)	107 (22.4)	73 (17.9)		
Age, years	72 (71–73)	71 (70–72)	73 (72–74)	**0.0001**	Mann-Whitney
Age (cutoff), n (%)				**0.0001**	Fisher
<70	340 (38.4)	211 (44.2)	129 (31.6)		
≥70	545 (61.6)	266 (55.8)	279 (68.4)		
Previous RF, n (%)	195/770 (25.3)	127/421 (30.2)	68/349 (19.5)	**0.0008**	Fisher
Previous TACE, n (%)	309/770 (40.1)	179/421 (42.5)	130/349 (37.2)	0.1405	Fisher
Child-Pugh, n (%)				0.1229	Fisher
A	820 (92.7)	448 (93.9)	372 (91.2)		
B	65 (7.3)	29 (6.1)	36 (8.8)		
BCLC, n (%)				**0.0048**	Fisher
B	358 (40.5)	172 (36.1)	186 (45.6)		
C	527 (59.5)	305 (63.9)	222 (54.4)		
ECOG PS, n (%)				0.5253	χ^2
0	657 (74.2)	353 (74.0)	304 (74.5)		
1	209 (23.6)	116 (24.3)	93 (22.8)		
≥2	19 (2.2)	8 (1.7)	11 (2.7)		
Neutrophils, /μL	3,072 (2,938–3,220)	2,880 (2,756–3,081)	3,258 (3,084–3,414)	**0.0105**	Mann-Whitney
Lymphocytes, /μL	1,199 (1,138–1,240)	1,161 (1,076–1,220)	1,234 (1,170–1,319)	0.0810	Mann-Whitney
Lymphocytes (cutoff), n (%)	n = 791	n = 421	n = 370	0.1453	Fisher
<950/μL	250 (31.6)	143 (34.0)	107 (28.9)		
≥950/μL	541 (68.4)	278 (66.0)	263 (71.1)		
NLR	2.67 (2.56–2.81)	2.63 (2.52–2.88)	2.69 (2.49–2.87)	0.6214	Mann-Whitney
NLR (cutoff), n (%)	n = 791	n = 421	n = 370	0.3863	Fisher
<3	464 (58.7)	253 (60.1)	211 (57.0%)		
≥3	327 (41.3)	168 (39.9)	159 (43.0)		
Platelets, /nL	143 (138–150)	139 (133–146)	150 (140–158)	**0.0439**	Mann-Whitney
Eosinophils, /μL	119 (109–140)	129 (110–155)	110 (98–137)	0.4180	Mann-Whitney
Eosinophils (cutoff), n (%)	n = 203	n = 124	n = 79	0.4885	Fisher
≥70/μL	158 (77.8)	94 (75.8)	64 (81.0)		
<70/μL	45 (22.2)	30 (24.2)	15 (19.0)		
Albumin, g/dL	3.71 (3.70–3.80)	3.80 (3.80–3.90)	3.70 (3.60–3.70)	**0.0001**	Mann-Whitney
Albumin (cutoff), n (%)	n = 875	n = 474	n = 401	0.0984	Fisher
≥3.5 g/dL	625 (71.4)	350 (73.8)	275 (68.6)		
<3.5 g/dL	250 (28.6)	124 (26.2)	126 (31.4)		
Bilirubin, mg/dL	0.8 (0.8–0.8)	0.8 (0.8–0.8)	0.8 (0.7–0.8)	0.8667	Mann-Whitney
Bilirubin (cutoff), n (%)	n = 883	n = 476	n = 407	0.7184	Fisher
>1 mg/dL	286 (32.4)	157 (33.0)	129 (31.7)		
≤1 mg/dL	597 (67.6)	319 (67.0)	278 (68.3)		

Table 2 (continued)

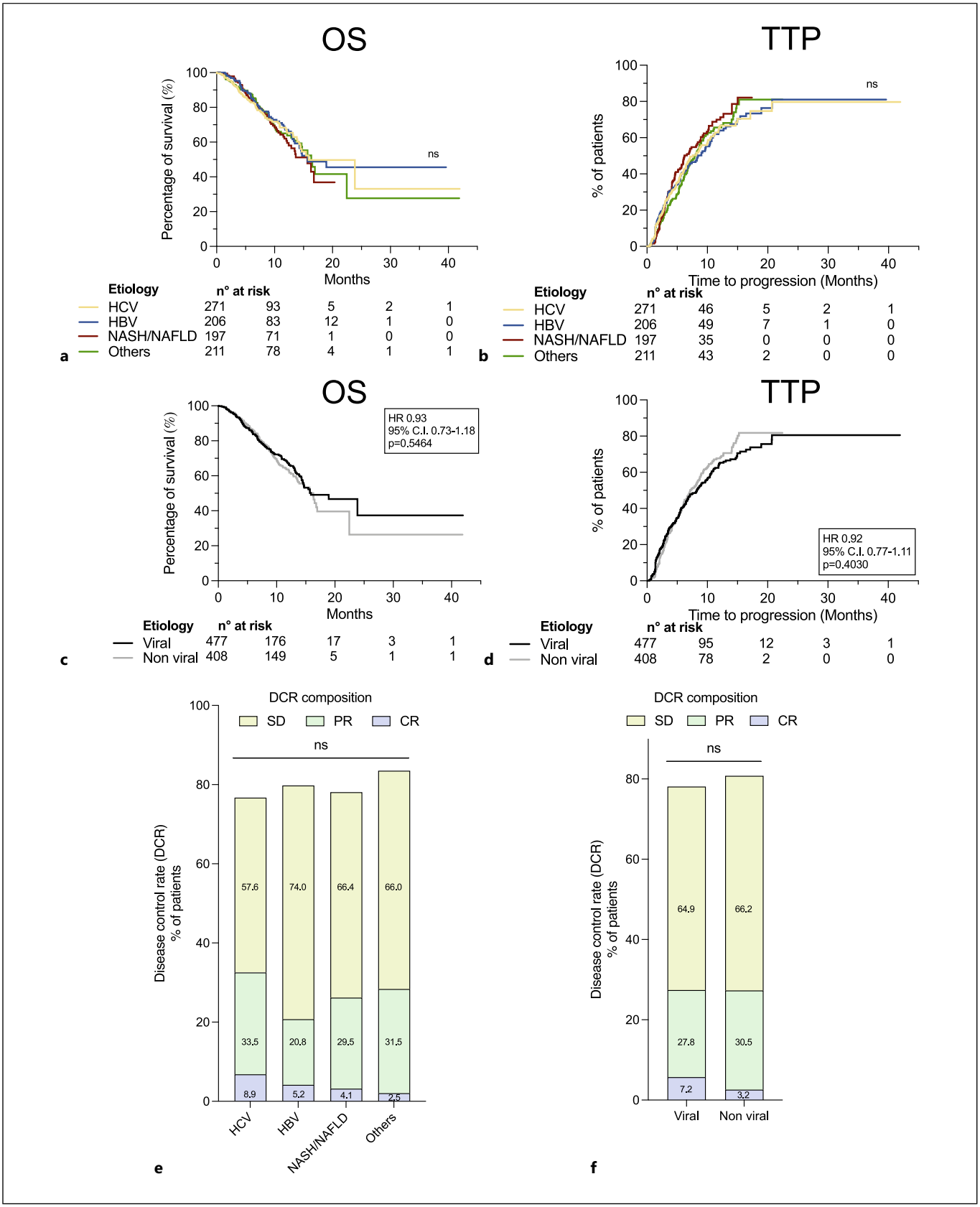
Variable	Total (n = 885)	Viral (n = 477)	Nonviral (n = 408)	p value	Test
ALBI	−3.24 (−3.29 to −3.20)	−3.33 (−3.42 to −3.29)	−3.16 (−3.21 to −3.12)	**0.0001**	Mann-Whitney
ALBI grade, n (%) Grade 1 Grade 2	n = 875 802 (91.7) 73 (8.3)	n = 474 439 (92.6) 35 (7.4)	n = 401 363 (90.5) 38 (9.5)	0.2721	Fisher
Creatinine, mg/dL	0.80 (0.79–0.82)	0.80 (0.78–0.83)	0.81 (0.79–0.83)	0.8049	Mann-Whitney
AST, U/L	41 (39–42)	40 (37–42)	42 (39–45)	0.3450	Mann-Whitney
AST (cutoff), n (%) >65U/L ≤65U/L	n = 880 691 (78.5) 189 (21.5)	n = 473 373 (78.9) 100 (21.1)	n = 407 318 89	0.8054	Fisher
ALT, U/L	28 (27–31)	27 (26–30)	30 (27–33)	0.2842	Mann-Whitney
ALT (cutoff), n (%) >40 U/L ≤40 U/L	 614 (69.4) 271 (30.6)	 335 (70.2) 142 (29.8)	 279 (68.4) 129 (31.6)	0.5592	Fisher
ALP, U/L	152 (138–166)	147 (127–164)	158 (141–189)	0.1827	Mann-Whitney
ALP (cutoff), n (%) >125 U/L ≤125 U/L	n = 346 212 (61.3) 134 (38.7)	n = 200 119 (59.5) 81 (40.5)	n = 146 93 (63.7) 53 (36.3)	0.4367	Fisher
Tumor					
Portal vein thrombosis, n (%)	272 (30.7)	148 (31.0)	124 (30.4)	0.8838	Fisher
AFP, ng/mL	51 (33–59)	62 (50–99)	28 (15–51)	**0.0003**	Mann-Whitney
AFP (cutoff), n (%) ≥400 ng/mL <400 ng/mL	n = 879 262 (29.8) 617 (70.2)	n = 474 157 (33.1) 317 (64.9)	n = 405 105 (25.9) 300 (74.1)	**0.0219**	Fisher
Extrahepatic disease	321 (36.3)	200 (42.0)	121 (29.7)	**0.0002**	Fisher

Continuous data are reported as medians and 95% CI; categorical variables are reported as absolute counts and relative percentages within the total. When continuous variables had statistically significant AUC >0.5 at ROC analysis, cutoff were introduced to dichotomize them (see Methods). When data were not available for the entire study population for a certain variable, the numerosity of collected data is reported. Comparisons for each variable between viral and nonviral etiologies were performed with the indicated test. ROC, receiver operating characteristic; AUC, area under the curve.

radiofrequency ablation (HR 0.75, p = 0.0122), previous TACE (HR 0.76, p = 0.0068), and absence of portal vein thrombosis or major vascular invasion (HR 0.72, p = 0.0017) (online suppl. Fig. 1; Table 4).

At multivariate analysis performed with the same criteria as above, the same baseline parameters associated with a reduced risk of death were also prognostic for progression: AFP <400 ng/mL (HR 0.73, p = 0.0045), AST <65 U/L (HR 0.73, p = 0.0335), NLR <3 (HR 0.76, p = 0.0083), and ALBI grade 1 (HR 0.69, p = 0.0320), but not viral versus nonviral etiology (HR 0.95, p = 0.6429) (Fig. 2b and online suppl. Table 5). Of these, only AFP <400 ng/mL was associated with a reduced risk of progression in viral (p = 0.0457) and non-viral (p = 0.0096) patients at multivariate analyses of etiology-based subgroups, while NLR <3 was exclusively significant in viral patients (HR 0.69, p = 0.0104) and previous TACE in nonviral patients (HR 0.63, p = 0.0050).

Finally, despite the partial availability of data in the study cohort, we preliminarily explored the potential prognostic impact of eosinophil count (n = 203 patients) and ALP (n = 346 patients), the constituent variables, besides AFP, of the recently described α-FAtE score [21], in further multivariate analyses for the risk of death and progression incorporating these two variables besides the prognostic ones already identified from the previous analyses (online suppl. Tables 6, 7).



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Of note, both eosinophil count ≥70/μL and ALP ≤125 U/L resulted as prognostic markers of OS in the overall population (HR 0.56, $p = 0.0069$ and HR 0.61, $p = 0.0163$, respectively), but only the former resulted to be prognostic in the viral subgroup (HR 0.53, $p = 0.0272$; online suppl. Table 6) and the latter in the nonviral one (HR 0.48, $p = 0.0326$), suggesting a possible major relevance of immunological factors in viral etiologies and metabolic factors in nonviral ones. Consistently, eosinophil count ≥70/μL was associated to a reduced risk of progression in the overall population (HR 0.55, $p = 0.0010$) and in the viral subgroup (HR 0.47, $p = 0.0009$), but not in the nonviral one (HR 0.85, $p = 0.6188$) (online suppl. Table 7). Altogether, despite the high grade of similarity in readouts and prognostic factors of viral and nonviral patients treated with the first-line A + B, these differences could underlie different biological features according to etiology.

Treatment Toxicities of Atezolizumab plus Bevacizumab and Second-Line Treatments in Viral and Nonviral HCC

A + B toxicities occurred at similar rates in viral and nonviral patients, including diarrhea (7.3% and 8.6%, respectively), fatigue (23.9% and 25.7%, respectively), proteinuria (28.5% and 27.0%, respectively), hypothyroidism (5.2% and 4.9%, respectively), other immune-related toxicities (13.4% and 13.0%, respectively), and other toxicities of any kind (19.1% and 19.9%, respectively) (Fig. 3a). However, hypertension was more commonly observed in viral patients (28.3% vs. 22.3%, $p = 0.0415$) while anorexia in nonviral ones (25.2% vs. 17.2%, $p = 0.0033$). The NCI-CTCAE grade occurrence of each toxicity did not significantly differ between viral and nonviral groups (χ^2 tests, all $p > 0.05$), suggesting the lack of any impact of etiology on the severity of treatment-related toxicities (Fig. 3a).

Finally, we investigated the access to second-line treatments at progression of viral and nonviral patients, finding no significant difference based on disease etiology ($p = 0.7153$, Fig. 3b). Overall, out of 464 patients in PD, 233 (50.2%) received a second-line treatment; among them, second-line treatments were undergone in 124 out of 244 (50.8%) viral patients and 109 out of 220 (49.5%) nonviral patients in PD.

Regarding the type of a second-line treatment received, no statically significant differences were observed in nonviral and viral patients ($p = 0.65$, Fig. 3b), with lenvatinib representing the most used second-line treatment (38.5% and 33.9%, respectively), followed by sorafenib (18.3% and 18.5%, respectively) and TACE (12.8% and 10.5%, respectively). Cabozantinib represented 10.1% and 9.7% of second-line treatments of nonviral and viral patients, respectively; ramucirumab 7.3% and 4.8%; any ICI 0.9% and 4.0%; regorafenib 0.9% and 1.6%; other treatments 11.0 and 16.9%. Importantly, the sub-analysis for OS of patients progressed to the first-line A + B showed a significant reduction in the risk of death in those who received a second-line treatment compared to those who did not (HR 0.40, 95% CI 0.30–0.53, $p < 0.0001$) regardless of etiology (no second-line, viral vs. nonviral HR 1.20, 95% CI 0.84–1.70, $p = 0.3114$; second-line, viral vs. nonviral HR 1.17, 95% CI 0.77–1.79, $p = 0.4588$; Fig. 3c). Thus, underlying liver disease etiology does not affect the probability to access and the outcome of second-line treatment after progression to A + B.

Discussion

Here, we showed that in a large, multicenter population of $n = 885$ HCC patients treated with the first-line A + B from Asia and Europe, even though with a major contribution from the former, underlying viral etiologies were not significantly correlated to better OS, TTP, or DCRs over nonviral etiologies in a real-world scenario. Our results fit with the post hoc analysis of IMbrave-150 by Espinoza and colleagues on $n = 279$ patients enrolled in the trial [5], and concur on the non-superiority of A + B in viral compared to nonviral

Fig. 1. Underlying liver disease etiology does not significantly impact response and survival of HCC patients treated with atezolizumab plus bevacizumab. Kaplan-Meier survival curves of overall survival (OS) (**a**) and time-to-progression (TTP) (**b**) of atezolizumab plus bevacizumab-treated patients classified for underlying liver etiologies (HBV, HCV, NASH/NAFLD, other; log-rank Mantel-Cox test with Bonferroni correction). Kaplan-Meier survival curves of OS (**c**) and TTP (**d**) of atezolizumab plus bevacizumab-treated patients classified for underlying liver etiologies grouped in viral and nonviral (log-rank Mantel-Cox test). Disease control rates of atezolizumab plus bevacizumab as per mRECIST criteria across the four different etiology groups (**e**) or grouped into viral and nonviral etiology (**f**). Differences in the proportion of patients achieving either disease control or not in the four groups were assessed using the χ^2 test ($p = 0.3457$), while in viral versus nonviral patients with Fisher's exact test ($p = 0.3430$). SD, stable disease; PR, partial response; CR, complete response.

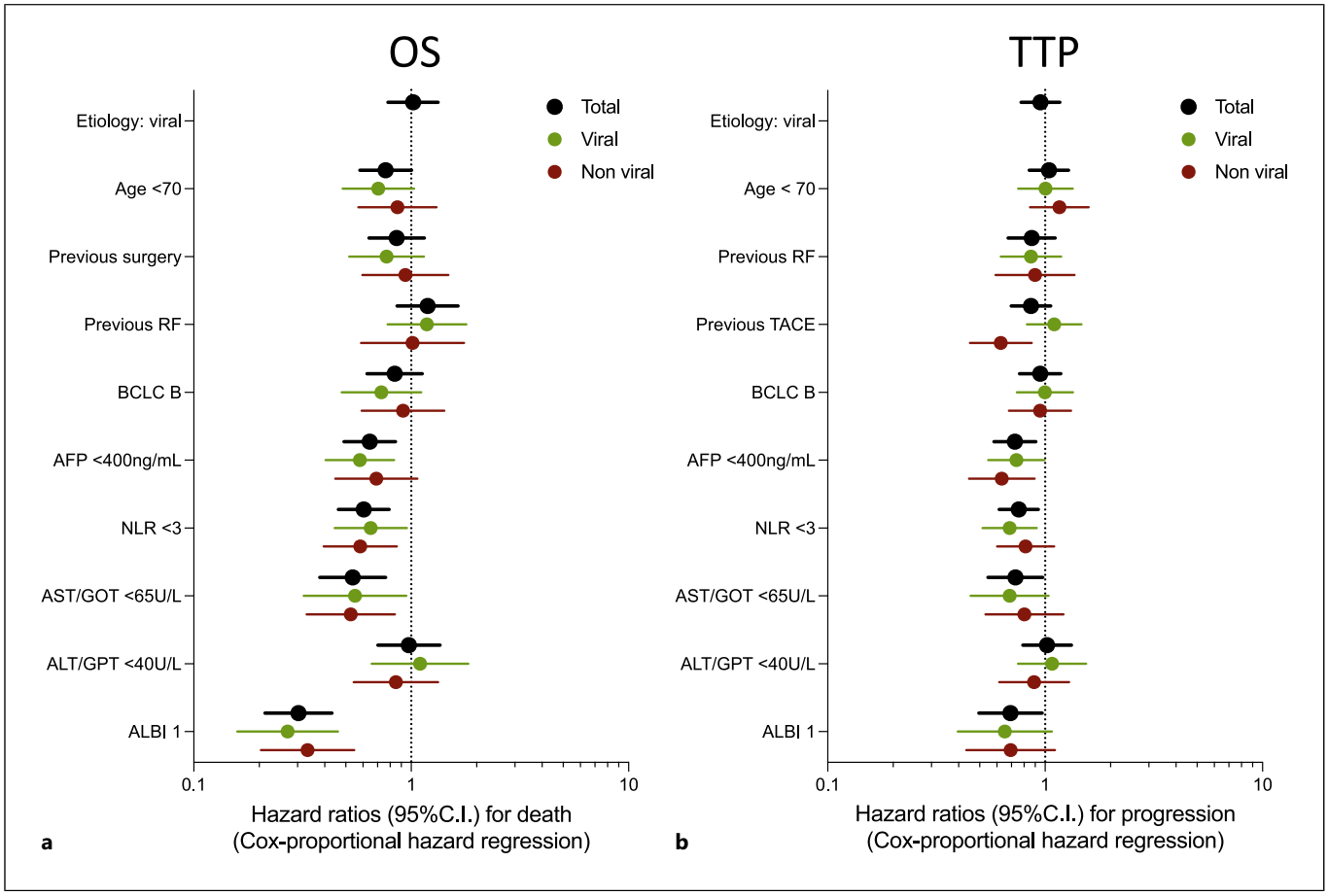

Fig. 2. Baseline clinical and laboratory prognostic factors of HCC patients treated with atezolizumab plus bevacizumab according to etiology. Forest plot representing the hazard ratios (HRs) and 95% CI of baseline variables of HCC patients treated with atezolizumab plus bevacizumab for the risk of death (**a**) and progression (**b**) (results from multivariate analysis with Cox proportional-hazards regression model; raw data in online suppl. Table 3 and 5). HR on entire population, viral and nonviral subpopulation are depicted in color-code.

etiologies. HCV etiology was slightly over-represented in our study cohort compared to [5] (30.6% vs. 25.1% of the total), while HBV under-represented (23.3% vs. 38.7% of the total), likely due to geographical and epidemiological differences. Among nonviral etiology, our study cohort almost completely overlap that of [5], with NASH/NAFLD representing 48.3% versus 46.5% of nonviral patients (22.2% vs. 16.8% of total) and alcoholic liver disease and other etiologies representing 51.7% versus 53.5% of nonviral patients (23.8% vs. 19.4% of total).

Despite this further clinical evidence of similar performance of A + B in HCC patients with different etiologies, it is conceivable that NASH-related HCC may be immunologically and biologically different from viral-related HCC [11]. Indeed, an enrichment of gene expression signatures related to oxidative stress and inflammation along with exhaustion of CD8+ T cells has been characterized in NASH-related HCC [22, 23]. Furthermore, pathogen-associated antigens have been described to be immune-dominant antigens for effective antitumor T-cell response that could be unleashed by immunotherapy in viral-related HCC more likely than nonviral one [24–26]. The significant imbalance between the inflammatory microenvironment and immune exhaustion programs active in NASH-related HCC could represent a resistance mechanism to different immunotherapeutic approaches.

These biological features can also account for the few differences in prognostic factors for OS and/or TTP to A + B identified in viral compared to nonviral patients in the present work, despite the similar survival outcomes that

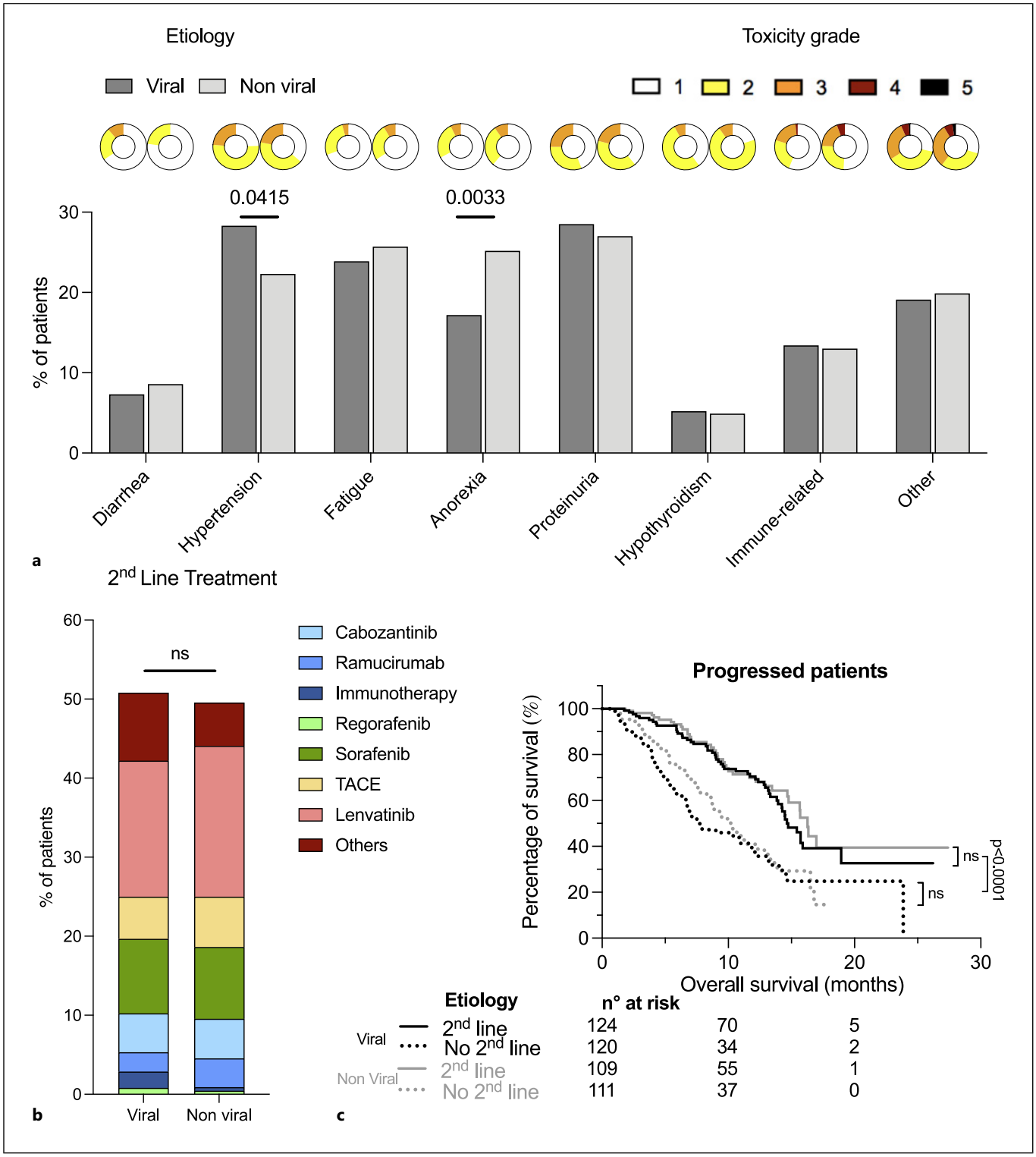

Fig. 3. HCC etiology does not impact atezolizumab plus bevacizumab toxicity profile nor access and outcome of second-line treatments. **a** Fraction of viral and nonviral patients experiencing the reported toxicity (bar plot, Fisher's exact test for each toxicity) and the respective NCI-CTCAE grade composition (donut chart, χ^2 tests retrieved $p > 0.05$ in every comparison). **b** Comparison of the fraction of viral and nonviral patients receiving a second-line active treatment of any kind ($p = 0.7153$, Fisher's exact test) and the fraction of specific treatment received is color-coded ($p = 0.6495$, χ^2 test). **c** Kaplan-Meier survival curves of overall survival (OS) of viral and nonviral patients progressed to the first-line atezolizumab plus bevacizumab that either received or not any a second-line treatment (log-rank Mantel-Cox test with Bonferroni correction).

were achieved in the two groups. Indeed, NLR and, even if more preliminarily due to the partial availability of data, eosinophil count, reflecting circulating immune composition, were identified as putative prognostic factors only in viral patients. These findings, even though not conclusive in absence of prospective validation, suggest a possible major relevance of immunological processes in viral-related HCC.

The latest international guidelines on HCC management recommend atezolizumab plus bevacizumab or durvalumab plus tremelimumab as the first-line systemic treatment of choice, regardless of etiology [27–29]. Only in case of contraindications to or unfeasibility of these two immunotherapy approaches, TKIs (namely sorafenib and lenvatinib) can be proposed as the first-line systemic treatment. The impact of HCC etiology on TKI response goes beyond the purpose of the present work, but few considerations raise from studies in which immunotherapy has been compared to TKIs and subgroup analyses based on etiology have been reported.

First, in the early metanalysis of IMbrave-150, CheckMate-459, and Keynote-240 with ICIs of PD-1/PD-L1 axis, no significant advantage of immunotherapy over control group was observed in nonviral patients [11]. Second, retrospective real-world evidence [7, 8] and a previous IMbrave-150 post hoc analysis [4] suggest that TKIs may perform better in patients with NASH/NAFLD than viral etiology, possibly resulting even more active in this specific subgroup of patients compared to A + B [9].

Altogether, these data could indicate that A + B does not significantly underperform in nonviral patients compared to viral ones, but rather that nonviral patients with metabolic liver-diseases achieve better outcomes when treated with TKIs compared to viral patients, supporting the possible existence of different biological features and treatment susceptibility according to etiology. Future perspective studies will be mandatory to test this hypothesis.

In a very recent metanalysis of 8 immunotherapy clinical trials for HCC, immunotherapy seems superior to the controls in both viral and nonviral patients [6]. The metanalysis included IMbrave-150 (A + B vs. sorafenib) [2, 4], Checkmate-459 (nivolumab vs. sorafenib) [10], Keynote-240 (pembrolizumab vs. BSC) [3], COSMIC-312 (cabozatinib plus atezolizumab vs. sorafenib) [30], HIMALAYA (tremelimumab plus durvalumab vs. sorafenib) [31], LEAP-002 (lenvatinib plus pembrolizumab vs. lenvatinib) [32, 33], RATIONALE-001 (tislelizumab vs. sorafenib) [34], and NCT03764293 (camrelizumab+apatinib vs. sorafenib) [35]. Of note, besides the heterogeneity of immunotherapy approaches included in the metanalysis, also controls were heterogeneous by composition, including patients treated with sorafenib, lenvatinib, and BSC. Furthermore, at the individual trial level, HIMALAYA was the only study showing a significant superiority of immunotherapy over control in nonviral patients. Interestingly, HIMALAYA is the only trial investigating also a CTLA-4-directed ICI, suggesting that the immunological background of nonviral HCC could limit response to PD-1/PD-L1 blockade, but benefit more from CTLA-4 inhibition [36]. Indeed, CTLA-4 ICIs exert part of their action in tumor-draining lymph nodes, possibly resulting less susceptible to the variability of the tumor microenvironment of HCC arisen from different liver disease etiologies [37, 38]. Besides blocking immune checkpoint molecules on effector CD8 T cells, CTLA-4 inhibition targets and counteracts the activity of T regulatory cells, which have been described to be major contributor to NASH-related carcinogenesis [39].

Among the limitations of the present work, its retrospective nature may have affected the completeness of data and the uniformity of the study population due to selection bias. Moreover, the evaluation of TTP may suffer from reproducibility issues due to the multicentric and multinational nature of the work since no centralized imaging review was included in the study protocol and the tumor assessment was made according to the clinical protocol of each institute. Another possible drawback concerns treatment interruptions and their putative impact on disease outcome of patients with different etiologies. Furthermore, despite the multicenter nature of the work, most of the patients in the study cohort were of Asiatic origin. Finally, co-existence of multiple etiologies in the same patient may have represented a confounding effect, and future studies should be designed to address this aspect.

Since retrospective data with no prospective validation could not be considered conclusive, etiology of underlying liver disease may still be worth of consideration in the general evaluation, along with other clinical and pathological features, in the decision-making process for patients affected by advanced HCC. Direct comparison of different therapies can unmask biological and susceptibility differences in specific subgroups of patients, e.g., based on etiology that would be otherwise unapparent when performing subgroup analyses of individual treatments.

Preclinical models can offer a rationale to postulate clinical hypotheses, while post hoc analyses and real-world retrospective studies serve as valuable tools to support or challenge these hypotheses. However, the design of prospective trials with preplanned stratification

for etiology is essential to robustly verify them and to ultimately help defining the role of etiology in the treatment of advanced HCC patients.

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Dr. Takashi Niizeki and Dr. Noritomo Shimada were not available to confirm co-authorship, but the corresponding author Dr. Casadei-Gardini Andrea affirms that Dr. Takashi Niizeki and Dr. Noritomo Shimada contributed to the paper, had the opportunity to review the final version to be published and guarantees authors Dr. Takashi Niizeki and Dr. Noritomo Shimada's co-authorship status and the accuracy of the author contribution and conflict of interest statements.

Statement of Ethics

This study protocol was reviewed and approved by San Raffaele Ethical Committee, approval number 113/INT/2021. Written informed consent for treatment and participation in this study was obtained from all participants in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

Andrea Casadei-Gardini has received grants and personal fees from MSD, Eisai, Bayer and is an advisor for MSD, Eisai, Bayer, Bristol-Myers Squibb, AstraZeneca and GSK. Atsushi Hiraoka received lecture's fees from Chugai, Lilly, AstraZeneca. Fabian Finkelmeier has received travel support from Ipsen, and speaker's fees from AbbVie, MSD, Ipsen, Eisai and Fresenius. Gianluca Masi is an advisor for Roche, MSD, Eisai. Giuseppe Cabibbo is a consultant for Roche, AstraZeneca, Eisai, MSD. Hidenori Toyoda has received grants and personal fees from Gilead, AbbVie, Eisai, Fujifilm, Teruma, Kowa, Takeda. Ho Yeong Lim is an advisor for Roche, Eisai, AstraZeneca, Bayer. Hong Jae Chon has advisory role for Roche, Eisai, Bayer, ONO, MDS, BMS, Sanofi, Servier, AstraZeneca, Silajen, Menarini, GreenCross Cell; received speaker's fee and research grants from Roche, Eisai, Bayer, BMS, Sanofi, Dong-A ST, BORYUNG, Inno.N, Hanmi, YUHAN. Josè Presa is an advisor for Gilead, AbbVie, Roche, AstraZeneca, Giszi, Advaus. Mario Scartozzi received grants and personal fees from MSD, Merck, Servier, Novartis, AstraZeneca. Masatoshi Kudo received lecture's fees from Chugai Pharmaceutical, Eisai, Eli Lilly Japan, Takeda Pharmaceutical; is an advisor for F. Hoffmann-La Roche, AstraZeneca, Chugai Pharmaceutical, Eisai; and received grants from Otsuka Pharmaceutical, Taiho Pharmaceutical, Chugai Pharmaceutical, GE Healthcare Japan Corporation, Eisai, AbbVie, EA Pharma. Massimo Iavarone received grants and personal fees from MSD, Gilead, AstraZeneca, Bayer, Roche, Ipsen, Eisai. Takeshi Hatanaka received lecture's fees from Eisai. The other coauthors have no conflict of interest to disclose.

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Author Contributions

Federico Rossari, Andrea Casadei-Gardini, and Margherita Rimini: conception and design, acquisition of data (acquired and managed patients), analysis and interpretation of data, and manuscript writing.

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Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request.

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